

Inventors: Rajotte et al.  
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#### CURRENT STATUS OF ALL CLAIMS

This listing of claims will replace all prior versions, and listings, of claims in the application:

Claims 1-4 (cancelled)

Claim 5 (currently amended) A method of selectively directing a moiety to lung endothelium in a subject, comprising administering to said subject a conjugate comprising a moiety linked to a MDP-binding homing molecule ~~identified by the method of claim 1,~~

wherein said MDP-binding homing molecule is identified by a method comprising contacting membrane dipeptidase (MDP) with one or more molecules and determining specific binding of a molecule to said MDP,

~~whereby~~wherein said moiety is selectively directed to lung endothelium in said subject[[.]],

and wherein said homing molecule has the ability to specifically bind the MDP classified as EC 3.4.13.19.

Claim 6 (original) The method of claim 5, wherein said MDP-binding homing molecule is a peptide comprising the sequence:

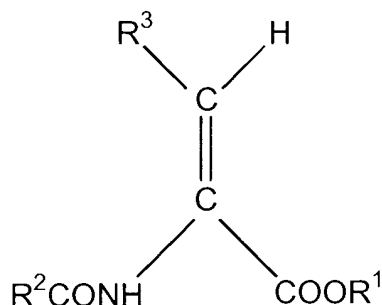
$X_1$ -G-F-E- $X_2$  (SEQ ID NO: 17)

wherein  $X_1$  and  $X_2$  each is 1 to 10 independently selected amino acids.

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Claim 7 (original) The method of claim 6, wherein said MDP-binding homing peptide comprises a sequence selected from the group consisting of CGFECVRQCPERC (SEQ ID NO: 1) and CGFELETC (SEQ ID NO: 2).

Claim 8 (withdrawn) The method of claim 5, wherein said MDP-binding homing molecule comprises the following Structure 1:



wherein R<sup>2</sup> and R<sup>3</sup> are hydrocarbon radicals in the range respectively of 3-10 and 1-15 carbon atoms; in either one of these R<sup>2</sup> or R<sup>3</sup> hydrocarbon chains 1-6 hydrogens may be replaced by halogens or a nonterminal methylene may be replaced by oxygen or sulfur, including oxidized forms of the latter; additionally, a terminal hydrogen in R<sup>3</sup> can also be replaced by hydroxyl or thiol, which may be acylated or carbamoylated; or the hydrogen can be replaced by amino, which may be derivatized as in an acylamino, ureido, amidino, guanidino, or alkyl or substituted amino group, including quaternary nitrogen grouping; or, there may be replacement by acid groups such as carboxylic, phosphonic or sulfonic acid groups or esters or amides thereof, or cyano; or

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combinations thereof, such as a terminal amino acid grouping; and  $R^1$  is hydrogen or lower alkyl ( $C_{1-6}$ ) or dialkylaminoalkyl, or a pharmaceutically acceptable cation.

Claim 9 (withdrawn) The method of claim 8, wherein said MDP-binding homing molecule is 7-(L-2-amino-2-carboxyethylthio)-2-(2,2-dimethylcyclopropane carboxamido)-2-heptenoic acid.

Claim 10 (withdrawn) The method of claim 8, wherein  $R^2$  is branched alkyl or cycloalkyl with a limitation that the carbon adjacent to the carbonyl cannot be tertiary.

Claim 11 (withdrawn) The method of claim 10, wherein  $R^3$  is n-alkyl (1-9 carbons) or n-alkyl (1-9 carbons) having a terminal substituent which is a quaternary nitrogen, amine derivative or amino acid derived group.

Claim 12 (withdrawn) The method of claim 11, wherein  $R^2$  is 2,2-dimethylcyclopropyl or 2,2-dichlorocyclopropyl and  $R^3$  is a hydrocarbon chain of 3 to 7 carbon atoms without a terminal substituent or having a terminal substituent which is trimethylammonium, amidino, guanidino or 2-amino-2-carboethylthio.

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Claim 13 (withdrawn) The method of claim 12, wherein said MDP-binding homing molecule is selected from the group consisting of:

Z-2-(2,2-dimethylcyclopropanecarboxamido)-8-trimethylammonium hydroxide-2-octenoic acid inner salt;

Z-2-(2,2-dichlorocyclopropanecarboxamido)-8-trimethylammonium hydroxide-2-octenoic acid inner salt;

Z-2-(2,2-dimethylcyclopropanecarboxamido)-8-guanidino-2-octenoic acid;

Z-2-(2,2-dimethylcyclopropanecarboxamido)-8-guanidino-2-octenoic acid;

Z-2-(2,2-dimethylcyclopropanecarboxamido)-8-ureido-2-octenoic acid;

Z-8-(1-2-amino-2-carboxyethylthio)-2-(2,2-dimethylcyclopropanecarboxamido)-2-octenoic acid;

Z-2-(2,2-dimethylcyclopropanecarboxamido)-2-octenoic acid (racemic and dextrorotatory forms);

Z-2-(2,2-dichlorocyclopropanecarboxamido)-2-octenoic acid;

7-(L-2-amino-2-carboxyethylthio)-2-(2,2-dimethylcyclopropanecarboxamido)-2-heptenoic acid; and

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6-(L-2-amino-2-carboxyethylthio)-2-(2,2-dimethylcyclopropanecarboxamido)-2-hexenoic acid.

Claim 14 (withdrawn) The method of claim 5, wherein said moiety is a gene therapy vector.

Claim 15 (withdrawn) The method of claim 5, wherein said moiety is a drug.

Claim 16 (withdrawn) A method of reducing or preventing lung metastasis in a subject having cancer, comprising administering to said subject a membrane dipeptidase (MDP)-binding homing molecule.

Claim 17 (withdrawn) The method of claim 16, wherein said MDP-binding homing molecule is a lung homing peptide comprising the sequence:

$X_1$ -G-F-E- $X_2$  (SEQ ID NO: 17)

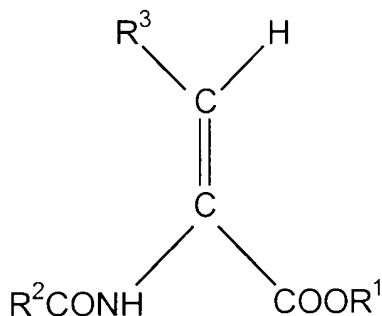
wherein  $X_1$  and  $X_2$  each is 1 to 10 independently selected amino acids.

Claim 18 (withdrawn) The method of claim 17, wherein said MDP-binding homing peptide comprises a sequence selected from the group consisting of CGFECVRQCPERC (SEQ ID NO: 1) and CGFELETC (SEQ ID NO: 2).

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Claim 19 (withdrawn) The method of claim 18, wherein said MDP-binding homing peptide is a peptide selected from the group consisting of CGFECVRQCPERC (SEQ ID NO: 1) and CGFELETC (SEQ ID NO: 2).

Claim 20 (withdrawn) The method of claim 16, wherein said MDP-binding homing molecule comprises the following Structure 1:



wherein R<sup>2</sup> and R<sup>3</sup> are hydrocarbon radicals in the range respectively of 3-10 and 1-15 carbon atoms; in either one of these R<sup>2</sup> or R<sup>3</sup> hydrocarbon chains 1-6 hydrogens may be replaced by halogens or a nonterminal methylene may be replaced by oxygen or sulfur, including oxidized forms of the latter; additionally, a terminal hydrogen in R<sup>3</sup> can also be replaced by hydroxyl or thiol, which may be acylated or carbamoylated; or the hydrogen can be replaced by amino, which may be derivatized as in an acylamino, ureido, amidino, guanidino, or alkyl or substituted amino group, including quaternary nitrogen grouping; or, there may be replacement by acid groups such as carboxylic, phosphonic

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or sulfonic acid groups or esters or amides thereof, or cyano; or combinations thereof, such as a terminal amino acid grouping; and  $R^1$  is hydrogen or lower alkyl ( $C_{1-6}$ ) or dialkylaminoalkyl, or a pharmaceutically acceptable cation.

Claim 21 (withdrawn) The method of claim 20, wherein said MDP-binding homing molecule is 7-(L-2-amino-2-carboxyethylthio)-2-(2,2-dimethylcyclopropane carboxamido)-2-heptenoic acid.

Claim 22 (withdrawn) The method of claim 20, wherein  $R^2$  is branched alkyl or cycloalkyl with a limitation that the carbon adjacent to the carbonyl cannot be tertiary.

Claim 23 (withdrawn) The method of claim 22, wherein  $R^3$  is n-alkyl (1-9 carbons) or n-alkyl (1-9 carbons) having a terminal substituent which is a quaternary nitrogen, amine derivative or amino acid derived group.

Claim 24 (withdrawn) The method of claim 23, wherein  $R^2$  is 2,2-dimethylcyclopropyl or 2,2-dichlorocyclopropyl and  $R^3$  is a hydrocarbon chain of 3 to 7 carbon atoms without a terminal substituent or having a terminal substituent which is trimethylammonium, amidino, guanidino or 2-amino-2-carboethylthio.

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Claim 25 (withdrawn) The method of claim 24, wherein said MDP-binding homing molecule is selected from the group consisting of:

Z-2-(2,2-dimethylcyclopropanecarboxamido)-8-trimethylammonium hydroxide-2-octenoic acid inner salt;

Z-2-(2,2-dichlorocyclopropanecarboxamido)-8-trimethylammonium hydroxide-2-octenoic acid inner salt;

Z-2-(2,2-dimethylcyclopropanecarboxamido)-8-guanidino-2-octenoic acid;

Z-2-(2,2-dimethylcyclopropanecarboxamido)-8-guanidino-2-octenoic acid;

Z-2-(2,2-dimethylcyclopropanecarboxamido)-8-ureido-2-octenoic acid;

Z-8-(1-2-amino-2-carboxyethylthio)-2-(2,2-dimethylcyclopropanecarboxamido)-2-octenoic acid;

Z-2-(2,2-dimethylcyclopropanecarboxamido)-2-octenoic acid (racemic and dextrorotatory forms);

Z-2-(2,2-dichlorocyclopropanecarboxamido)-2-octenoic acid;

7-(L-2-amino-2-carboxyethylthio)-2-(2,2-dimethylcyclopropanecarboxamido)-2-heptenoic acid; and



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6-(L-2-amino-2-carboxyethylthio)-2-(2,2-dimethylcyclopropanecarboxamido)-2-hexenoic acid.

Claim 26 (withdrawn) The method of claim 16, wherein said MDP-binding homing molecule is an MDP inhibitor.

Claim 27 (withdrawn) The method of claim 26, wherein said MDP inhibitor exhibits a  $K_i$  against MDP of at most 1000 nM.

Claim 28 (withdrawn) The method of claim 27, wherein said MDP inhibitor exhibits a  $K_i$  against MDP of at most 100 nM.

Claim 29 (withdrawn) The method of claim 28, wherein said MDP inhibitor exhibits a  $K_i$  against MDP of at most 1 nM.

Claim 30 (withdrawn) The method of claim 16, wherein said cancer is melanoma.